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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/635,429	08/10/2000	Sachiko Machida	195617US0X	6992

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	6

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/635,429	MACHIDA ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT OF AMENDMENT, REMARKS AND STATUS OF THE CLAIMS

1. The amendment and remarks filed 5/31/02 are acknowledged, entered and considered. In view of Applicant's request claims 1-8 have been canceled and claims 9-30 have been added. Thus, claims 9-30 are now pending in the application. The rejections under 35 U.S.C. 112, second paragraph and 35 U.S.C. 102(b) over the prior art of record are withdrawn in view of Applicant's amendment, remarks and cancellation of the claims. However, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained for newly submitted claims 9-30.

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Newly submitted claims 9-30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Daugherty et al. (The Journal of Biological Chemistry, Vol. 273, No. 51, pp. 33961-33971, December 18, 1998) taken with Takaha et al. (The Journal of Biological Chemistry, Vol. 271, No. 6, pp. 2902-2908, February 9, 1996).

The reference of Daugherty et al. as discussed in the previous Office action under the rejection of 102(b) discloses the application of an artificial chaperone refolding methods to porcine heart citrate synthase (CS), carbonic anhydrase B (CAB) and lysozyme by combining cyclic saccharide such as cyclodextrin and detergents such as POE(10)L, Triton X-100, SDS, etc. i.e., nonionic and ionic detergents (See e.g. pages 33961 and 33963-33964). It is noted that the reference does not recite cyclic saccharide cycloamylose as currently claimed in claims 9 and 13; however, the reference recites cyclodextrin which is defined as a high molecular weight cyclic α-1,4-glucan which is referred as cycloamylose and generally called α, β and γ cyclodextrin, respectively. Thus, it is known in the art that cyclodextrin is the same as cycloamylose. For support, See e.g., particularly the reference of Machida et al. at page 131 (Machida et al. FEBS Letters, 486 (2000) 131-135) which is attached as pertinent art. Thus, the reference of Daugherty et al. discloses the combination of cyclic saccharide cycloamylose and detergents such as polyoxyethylenic detergent or ionic detergent such as SDS are useful as artificial chaperone.

The reference also teaches the use of the artificial chaperone method of two steps, wherein the first step is to prevent aggregation of protein molecules by the formulation of protein-detergent complexes, in which hydrophobic regions of non-native protein molecules are shielded by detergent. The second step is the addition of cyclodextrin (cycloamylose) which initiates folding by stripping detergent from the protein-detergent complexes to facilitate the proper folding of protein into a correct higher-order structure with activity (See e.g. pages 33961, 33963-33964, 33966-33971 and Scheme I).

Although, the primary reference clearly teaches the combination of cyclic saccharide cycloamylose and detergents such as polyoxyethylenic or ionic detergents is useful as an artificial chaperone and method for diluting the denaturant thereof and method of refolding denatured protein into native state having an activity by using the artificial chaperone as claimed in newly submitted claims 9-30. However, the reference differs from claims 9-30 in not teaching the use of an artificial chaperone kit and the recitation of specific polymerization degree of cyclic saccharide cycloamylose. Nevertheless, the secondary reference of Takaha et al. teaches the determination of the degree polymerization of cycloamylose products by time of flight mass spectrometry analysis and by high performance anion-exchange chromatography following partial acid hydrolysis of purified cycloamylose molecules and was found to range from 17 to several hundred. The yield of cycloamylose increased with time and reached >95%. Hence, showing that the fraction containing cyclic glucans with degree of polymerization from 17 to several hundred, and as such overlaps with the claimed ranges of polymerization degrees of

claims 9, 11-13, 15-17, 19-20, 24 and 26--27. Thus, the secondary reference discusses the mechanism of the cyclization reaction, the possible role of the enzyme in starch metabolism, and the potential applications for cycloamylose (See e.g., page 2902). Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary reference to the primary reference because such features are known or suggested in the art, as seen in the secondary reference, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

In regard to the kit, the primary reference discloses an artificial chaperon formulation, however, from the cited references, it is conventional and within the ordinary skill in the art based upon the teachings of the combined references to have such kits/compositions as set forth in newly submitted claims 9-16 5-8 since the combined references teach using these compositions together in the same formulations that would have been found in the claimed compositions and/or kits to formulate compositions into a kit format because the claimed kit is tailored for use in the claimed artificial chaperone kit formulation comprising the composition claimed. Hence, it would have been obvious to package the composition required for the method into kit format of the well known commercial expediency of doing so.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ an artificial chaperone kit comprising cyclic saccharide cycloamylose and polyoxyethylenic detergent or cyclic saccharide

cycloamylose and ionic detergent and to a method for diluting the denaturant making the protein a denatured state by adding a specific detergent to a denatured protein, and preventing protein molecules from aggregation, thereafter adding cyclic saccharide cycloamylose, utilizing the inclusion ability thereof to strip detergent, accelerating the proper folding of protein into a correct higher-order structure activity, absence of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 103(a)

3. The rejection of newly submitted claims 9-30 under 35 U.S.C. 103(a) as being unpatentable over Daugherty et al. (The Journal of Biological Chemistry, Vol. 273, No. 51, pp. 33961-33971, December 18, 1998) taken with Takaha et al. (The Journal of Biological Chemistry, Vol. 271, No. 6, pp. 2902-2908, February 9, 1996).

Applicant's arguments filed 5/31/02 have been fully considered but they are not persuasive. Applicant asserts that nothing in the prior art suggests the recited cyclic saccharide cycloamylose having a polymerization degree of from 25 to 50 or 40 to 150 in combination with the recited detergents for refolding proteins. In addition, while it is known that β-cyclodextrin has an inclusion ability, an aqueous solution of this material is unstable due to low solubility and time-dependent decomposition. In contrast, the cyclic saccharide cycloamylose recited in the pending claims does not suffer from these defects. Accordingly, it is difficult to predict (1)

whether a cycloamylose with a specific degree of polymerization will actually include a specific substance or (2) whether the cycloamylose would exhibit any effect on protein refolding. These are unexpected result, not taught or suggested by the prior art is noted. However, contrary to Applicant's assertion, the combined teachings of the prior art employ an artificial chaperone kit comprising cyclic saccharide cycloamylose and polyoxyethylenic detergent or cyclic saccharide cycloamylose and ionic detergent and to a method for diluting the denaturant making the protein a denatured state by adding a specific detergent to a denatured protein, and preventing protein molecules from aggregation, thereafter adding cyclic saccharide cycloamylose, utilizing the inclusion ability thereof to strip detergent, accelerating the proper folding of protein into a correct higher-order structure activity.

Thus, for Applicant to validate the unexpected results of the cyclic saccharide cycloamylose recited in the pending claims does not suffer from these defects as asserted above, Applicant has to show a side by side comparison with unexpected results showing that there is a patentable difference between the instant invention's cyclic saccharide cycloamylose having a polymerization degree of from 25 to 50 or 40 to 150 in combination with the recited detergents for refolding proteins and the prior art cyclic saccharide cycloamylose. However, Applicant is cautioned that this is not an invitation to prolong the prosecution of after Final rejection.

Furthermore, a proper *prima facie* case of obviousness is overcome by evidence that the prior art teaches away from the invention, or by evidence that the claimed invention yields unexpected superior results. Applicant has not presented rebuttal evidence in order to prevail the

prima facie obviousness presented by the Examiner. Hence, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained for the same reasons discussed on the previous Office action as reiterated below:

Daugherty et al. disclose the application of an artificial chaperone refolding methods to porcine heart citrate synthase (CS), carbonic anhydrase B (CAB) and lysozyme by combining cyclic saccharide such as cyclodextrin and detergents such as POE(10)L, Triton X-100, SDS, etc. i.e., nonionic and ionic detergents (See e.g. pages 33961 and 33963-33964). It is noted that the reference does not recite cyclic saccharide cycloamylose as currently claimed in claims 9 and 13; however, the reference recites cyclodextrin which is defined as a high molecular weight cyclic α-1,4-glucan which is referred as cycloamylose and generally called α, β and γ cyclodextrin, respectively. Thus, it is known in the art that cyclodextrin is the same as cycloamylose. For support, See e.g., particularly the reference of Machida et al. at page 131 (Machida et al. FEBS Letters, 486 (2000) 131-135) which is attached as pertinent art. Thus, the reference of Daugherty et al. discloses the combination of cyclic saccharide cycloamylose and detergents such as polyoxyethylenic detergent or ionic detergent such as SDS are useful as artificial chaperone.

The reference also teaches the use of the artificial chaperone method of two steps, wherein the first step is to prevent aggregation of protein molecules by the formulation of protein-detergent complexes, in which hydrophobic regions of non-native protein molecules are shielded by detergent. The second step is the addition of cyclodextrin (cycloamylose) which initiates folding by stripping detergent from the protein-detergent complexes to facilitate the

proper folding of protein into a correct higher-order structure with activity (See e.g. pages 33961, 33963-33964, 33966-33971 and Scheme I). Although, the primary reference clearly teaches the combination of cyclic saccharide cycloamylose and detergents such as polyoxyethylenic or ionic detergents is useful as an artificial chaperone and method for diluting the denaturant thereof and method of refolding denatured protein into native state having an activity by using the artificial chaperone as newly submitted claims 9-30. However, the reference differs from claims 9-30 in not teaching the use of an artificial chaperone kit and the recitation of specific polymerization degree of cyclic saccharide cycloamylose. Nevertheless, the secondary reference of Takaha et al. teaches the determination of the degree polymerization of cycloamylose products by time of flight mass spectrometry analysis and by high performance anion-exchange chromatography following partial acid hydrolysis of purified cycloamylose molecules and was found to range from 17 to several hundred. The yield of cycloamylose increased with time and reached >95%. Hence, showing that the fraction containing cyclic glucans with degree of polymerization from 17 to several hundred, and as such overlaps with the claimed ranges of polymerization degrees of claims 9, 11-13, 15-17, 19-20, 24 and 26-27. Thus, the secondary reference discusses the mechanism of the cyclization reaction, the possible role of the enzyme in starch metabolism, and the potential applications for cycloamylose (See e.g., page 2902). Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary reference to the primary reference because such features are known or suggested in the art, as seen in the secondary reference, and including such features into the methods of the primary reference would

have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

In regard to the kit, the primary reference discloses an artificial chaperon formulation, however, from the cited references, it is conventional and within the ordinary skill in the art based upon the teachings of the combined references to have such kits/compositions as set forth in claims 9-16 since the combined references teach using these compositions together in the same formulations that would have been found in the claimed compositions and/or kits to formulate compositions into a kit format because the claimed kit is tailored for use in the claimed artificial chaperone kit formulation comprising the composition claimed. Hence, it would have been obvious to package the composition required for the method into kit format of the well known commercial expediency of doing so.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ an artificial chaperone kit comprising cyclic saccharide cycloamylose and polyoxyethylenic detergent or cyclic saccharide cycloamylose and ionic detergent and to a method for diluting the denaturant making the protein a denatured state by adding a specific detergent to a denatured protein, and preventing protein molecules from aggregation, thereafter adding cyclic saccharide cycloamylose, utilizing the inclusion ability thereof to strip detergent, accelerating the proper folding of protein into a correct higher-order structure activity, absence of sufficient objective factual evidence or unexpected results to the contrary.

The following is a new ground of rejection necessitated by Applicant's amendment.

CLAIMS REJECTION-35 U.S.C. § 112 [2nd] PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-16 are unclear regarding for the recitation "artificial chaperone kit...." since the claims are directed to the artificial chaperon kit *per se*; it is not clear what the artificial chaperon kit is supposed to achieve or have done. Appropriate clarification is required.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd.

App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 9, 13, 17 and 24 recite the broad recitation "from 40 to 150", and the claims also recite "from 25 to 50" which is the narrower statement of the range/limitation.

Claims 10, 14, 18 and 25 are indefinite in the recitation "....various detergents....." because it is not clear if Applicant intends a Markush format. If Applicant intends to use a Markush format, then, the Office recommends the use of the phrase".....selected from the group consisting of....." in listing species to ensure that the Markush group is "closed".

Claims 23 and 30 are indefinite and confusing in the recitation "wherein the protein has ....." because it is not clear if "the protein" refers to folded protein or denatured protein or to both. Appropriate clarification is required.

ACTION IS FINAL, NECESSITATED BY AMENDMENT

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONCLUSION AND FUTURE CORRESPONDENCE

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m.. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Mohamed/AAM

August 9, 2002